US009636337B2

(12) **United States Patent**
Bungard et al.

(10) **Patent No.: US 9,636,337 B2**
(45) **Date of Patent: May 2, 2017**

(54) **QUINOLINE CARBOXAMIDE AND QUINOLINE CARBONITRILE DERIVATIVES AS MGLUR2-NEGATIVE ALLOSTERIC MODULATORS, COMPOSITIONS, AND THEIR USE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/047,224**

(22) Filed: **Feb. 18, 2016**

(65) **Prior Publication Data**

US 2016/0158217 A1 Jun. 9, 2016

Related U.S. Application Data

(62) Division of application No. 14/356,080, filed as application No. PCT/US2012/062027 on Oct. 26, 2012, now Pat. No. 9,278,960.
(Continued)

(51) **Int. Cl.**
A61K 31/47 (2006.01)
A61K 31/506 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61K 31/47*** (2013.01); ***A61K 31/4709*** (2013.01); ***A61K 31/496*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC C07D 413/14; C07D 401/06
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,576,338 A 11/1996 Friesen et al.
7,960,409 B2 * 6/2011 Grimm C07D 401/06 514/314
(Continued)

FOREIGN PATENT DOCUMENTS

EP 0551831 A1 1/1993
WO WO9719928 A1 6/1997
(Continued)

OTHER PUBLICATIONS

EP Search Report, corresponding to PCT/US2012/062027, Apr. 8, 2015, 6 pages.
Hamana, M. et al., Reactions of 2-Phenyl-, 4-Phenyl-,and 2,4-Diphenyl-quinoline N-oxides with Acylating Agents, Faculty of Pharmaceutical Sciences, Kyushu University, Dec. 31, 1966, vol. 86(1), p. 59-66.
International Search Report and Written Opinion for PCT/US12/62027 dated Jan. 11, 2013.
Zhang et al., Investigation on Quantitative Structure Activity Relationships and Pharmacore 1-24 Modeling of a Series of mGluR2 Antagonists, Int J Mol Sci 12, pp. 5999-6023, 2011, p. 6001, para 2; p. 6002; para 1—p. 6014, para 1; p. 6015, Table 6.

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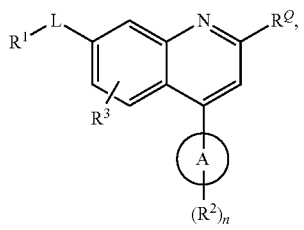
(57) **ABSTRACT**

The present invention provides quinoline carboxamide and quinoline carbonitrile compounds of formula (I)

(I)



wherein ring A, R^Q, -L-, R^1, n, R^2, and R^3 are as defined herein. The compounds of the invention are useful as non-competitive mGluR2 antagonists, or mGluR2 negative allosteric modulators (NAMs), and in methods of treating a patient (preferably a human) for diseases or disorders in which the mGluR2-NAM receptor is involved, including potentially Alzheimer's disease, cognitive impairment, schizophrenia and other mood disorders, pain disorders and sleep disorders, by administering to the patient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof. The invention is also directed to pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, (optionally in combination with one or more additional active ingredients), and a pharmaceutically acceptable carrier, and the use of the compounds and pharmaceutical compositions of the invention in the treatment of such diseases.

30 Claims, No Drawings